Scientific Abstract

STUDY TITLE:

A Phase I Trial of Ex Vivo NGF Gene Therapy for Alzheimer's Disease

INSTITUTION:

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Description:

This is an open label Phase I clinical trial of ex vivo NGF gene therapy for early Alzheimer's Disease (AD).

Basal forebrain cholinergic neurons undergo regular and severe degeneration in Alzheimer's disease (2, 4). Nerve Growth Factor (NGF) has shown robust efficacy in mouse, rat and large primate models in preventing the degeneration of these neurons (3, 5-11, 13, 15-24, 27-29, 31-34). When administered to aged rats or to rats with lesions of the basal forebrain cholinergic system, NGF treatment reverses memory deficits and ameliorates morphological and biochemical features of neuronal degeneration (3, 8-10, 18-21, 23, 33). When NGF is delivered to the aged primate brain by ex vivo gene therapy, it reverses spontaneous, age-related atrophy and degeneration of cholinergic neurons in the brain (24,30). The robust effects of NGF on cholinergic neurons in various brain models have been replicated by dozens of laboratories worldwide over the last decade. NGF has clearly been identified as a molecule of substantial potential for the treatment of

Alzheimer's disease (1, 12, 14, 25, 26, 35). However, a safe and effective method of delivering NGF to the brain has not been available until the recent development of gene therapy.

Over the past ten years, the principal investigators in this study have developed ex vivo gene therapy as a safe and effective method for the accurate delivery of NGF into the brain directly to the basal forebrain cholinergic neurons that are undergoing degeneration in Alzheimer's disease. Based upon an extensive base of pre-clinical safety and efficacy data in the rodent and primate, including long term in vivo gene expression data, we propose the present Phase I safety trial of ex vivo NGF gene therapy for Alzheimer's disease. Patients' fibroblasts will be genetically modified to produce and secrete human NGF in vitro, and will then be grafted into the brain to prevent neuronal degeneration and to augment neuronal function. Replication-incompetent MLV vectors lacking the *gag, pol* and *env* genes will be used to genetically modify cells. Since there are few if any dividing cells in the brain, the risk of inadvertently modifying anything other than the implanted cells will be very remote. Patients will receive autologous cell grafts.

Patients will receive one of four potential total volumes of cell implants in this study, in a "dose escalation" design. The "dose" of NGF delivered will be escalated by increasing the number of grafted cells. The cell density will not be varied because pre-clinical studies have established an optimal cell concentration that maximizes survival of the grafted cells and the ability to handle the cells prior to in vivo implantation. The number of grafting sites will not be varied because five injections of cells per side of the brain is optimal, based upon pre-clinical studies in primates, for delivering NGF to the full extent of the basal forebrain cholinergic system. However, the first two study patients will receive only unilateral cell implants to ensure the safety of the grafting procedure. All subsequent patients will receive bilateral cell implants. Greater numbers of grafts would be cumbersome and might compromise safety; fewer numbers of grafts might not fully reach all of the intended target neurons. Thus, the study will vary the gene therapy dose by varying the volume of implanted cells.

The study will be conducted over one year, although patients will be followed indefinitely at yearly intervals. In the first year of the study, patients will be evaluated two weeks, one month, three months, six months, nine months, and one year post-operatively. Patients will receive neuropsychological assessment one, three, six, nine, and twelve months post-operatively. The primary endpoint will be safety. Secondary outcome measures will include several established measures of cognitive function in Alzheimer's disease. Compliance will not be an issue since all cells will be surgically implanted. Patients with *early* stages of Alzheimer's disease will be targeted in this Phase I study for two reasons: 1) Enrollment in this study involves surgery and its associated risks, thus patients must fully understand the implications of their consent to enroll in the study. Such "informed consent" is only possible during the early stages of Alzheimer's disease. 2) Growth factor gene therapy aims to both *prevent* cell degeneration in the brain and to *augment* the function of remaining neurons. This objective is potentially most achievable in earlier stages of Alzheimer's disease.